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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/488,737	01/20/2000	Ling Lissolo	50019/008001	4843

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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/488,737	Lissolo et al
Examiner	**Art Unit**
Portner	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Mar 4, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Mar 4, 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see NOTE below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☒ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attachment.*

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see attachment.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*

   Claim(s) objected to: *none*

   Claim(s) rejected: *1, 3-7, 10, 11, 14-24, and 28-30*

   Claim(s) withdrawn from consideration: *25-27, 31, and 32*

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ .

10. ☐ Other:

For at least the following reasons the Amendment After Final has not been entered:

1. Claims 1, 10-11, 18-19 are proposed to be amended to no longer recite "consisting essentially of" and to recite "consisting of"; this raises a new issue.

2. Claims 14 and 15 are proposed to recite the phrase "between components of the sample"; this raises new issues with respect to antecedent basis for the term "components" in the claim; are the components of the sample the same as Helicobacter or the antibodies recited in the preamble, respectively?

3. Claim 19 is proposed to be amended to recite closed language, but claim 20 depends from claim 19 and recites "comprises", open language; this raises a new issue. Claim 20 also recites the phrase "fragment thereof" which broadens the scope of claim 19 which has an additional antigen and the fragments of claim 20 are not required to antigenic fragments, thus broadening the scope of claim 19 from which claim 20 depends.

4. Claim 29 is proposed to define the additional Helicobacter antigen to be a Helicobacter polypeptide antigen; this is a new combination of claim limitations for claim 29.

5. New claims 33-41 are proposed to be submitted After-Final which would necessitate new grounds of rejection.

Response to Remarks

6. Applicant's remarks at pages 11-14 are directed to newly submitted claim limitations not entered.

7. At page 14 (paragraph 3), Applicant requests the Office provide a rationale or evidence tending to show inherency, and asserts that this has not been done.

8. It is the position of the examiner that:

a. all of the references applied to the claims are directed to compositions of Helicobacter pylori protein antigens, methods of detecting Helicobacter antigens with anti-Helicobacter pylori antibodies, or compositions of anti-Helicobacter pylori antibodies.

b. The protein antigens claimed are membrane/surface associated proteins of Helicobacter pylori.

The applied references teach protein antigens obtained from the same strain of Helicobacter pylori as that used by Applicant,

i. specifically Alemohammad (ATCC 43579, col. 6, line 10);

or teach that the antigens are Helicobacter surface/membrane associated antigens:

ii. Husson et al produced an outer membrane fraction (see page 2695, col. 1, paragraph 3) from Helicobacter pylori cells; the reference discloses major outer membrane proteins (see page 2697, col. 1, paragraph 2), to include a 54 kDa heat shock protein (bottom of second paragraph, page 2697, col. 1).

iii. Calenoff disclosed Helicobacter pylori soluble protein antigens obtained from a whole cell sonicate the immunoreacted with antibodies stimulated thereto; the antigens were presented to the host and therefore must have been surface associated antigens for stimulation of an immune response.

iv. Ferrero et al showed antibodies stimulated prevented infection through binding of antibodies to surface/membrane associated antigens which resulted in reduced colonization (see Table 1, 10^1 inoculum dose).

v. The title of Bolin et al (1995) contains the phrase "species-specific monoclonal antibody with a surface-exposed protein"; Bolin produced an antibody to a Helicobacter membrane protein and identified the membrane protein as well.

vi. The title of Doig et al (1994) contains the phrase "Surface exposed outer membrane antigens of Helicobacter pylori".

vii. Pronovost et al utilized a whole cell sonicate which was centrifuged, the final pellet material being what the Helicobacter pylori proteins were purified (see col. 6, line 46-47; and also utilized Octyl B-D glucopyranoside in an extraction step to obtain Helicobacter membrane proteins (see col. 7, lines 6-20).

viii. Ruiz et al utilized Helicobacter pylori whole cells which present all membrane proteins for stimulation of an immune response, as well as purified urease as the immunogen for production of antibodies (see page 5, line 17, end of line);

9. Applicant questions the application of references with slightly different relative molecular weights and asserts "[T]he Office has not shown that the proteins of the present claims are necessarily present in the gels of the cited references, and any assertion that the probabilities or

possibilities might tend to point in this direction would not suffice in establishing a proper rejection.

10. It is the position of the examiner that the claimed invention is directed to several Helicobacter pylori membrane fraction associated protein antigens, the relative molecular weights of which were determined by SDS-PAGE gel electrophoresis. All of the applied prior art rejections addressed the scope of the claims directed to proteins of a relative molecular weight based upon SDS-PAGE or gel electrophoresis:

a. Husson et al (see page 2696, Figure 3, and page 2696, col. 1, paragraph 2);

b. Calenoff (see US Pat. 5,567,594; col. 11, lines 11-20, specifically line 19);

c. Ferrero et al (see page 6500, Figure 1; and page 6499, col. 2, first paragraph);

d. Bolin et al (see page 383, Figure 1, top of col. 1; and page 384, col. 1, paragraph 2, middle of paragraph, "30 kDa protein seems to be produced by all strains";

e. Doig et al (see Figures 3 and 4, page 4530 and Figures 5 and 6, page 4531);

f. Alemohammad (see US Pat.5,262,156, Figures 1 and 2; col. 7, lines 3-37; col. 6, lines 57-68);

g. Pronovost et al (US Pat. 5,814,455, col. 5, lines 27-29); and

h. Ruiz et al (WO94/06474, Figures 4a and 4b, SDS gel; page 4, lines 1-13).

The antigens disclosed by the applied prior art were obtained from the same or equivalent source, Helicobacter pylori, were antigenic or immunogenic proteins obtained from membrane preparations of H.pylori or were surface associated antigens that induced an immune response in a human patient, and evidenced the same or equivalent relative molecular weight as the instantly claimed Helicobacter pylori proteins. As no specific enzymatic or chemical functions, nor the

entire amino acid sequence for all of the claimed proteins have not been disclosed, by all comparable data, the Helicobacter pylori proteins of the prior art are the instantly claimed proteins. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art". Inherently the reference anticipates the now claimed invention

11. Applicant asserts that the "Helicobacter proteins that are somewhat close in size to the proteins and polypeptides of the present claims, and that is all."

12. It is the position of the examiner that the instantly claimed proteins with relative molecular weights are specifically taught by the applied references, specifically:

54 kDa

Doig et al disclose a 54 kDa protein (see page 4531,col. 2, paragraph 4, last line);

Ferrero et al disclose a 54 kDa protein (see page 6499, col. 2, first paragraph and Figure 1, page 6500);

Husson et al disclose a 54 kDa protein (page 2697, col. 1, paragraph 2, bottom of paragraph).

50 kDa

Doig et al disclose a 50 kDa protein (see pg 4531,col. 2, paragraph 4, last line; pg 4529, col. 2, paragraph 2).

32-35 kDa

Husson et al disclose a 33kDa protein (page 2697, col. 1, paragraph 2, middle of paragraph) which is within the claimed protein size range.

30 kDa

Doig et al disclose an antigen of 30kDa (see page 4531, col. 2, paragraph 2 and 4);

Bolin et al (see abstract, pg 381 and Figure 1, page 383, top of col. 1);

Husson et al disclose a 30 kDa protein (page 2697, col. 1, paragraph 2, middle of paragraph).

Thus the applied references disclose the claimed antigens of the recited numbers (relative molecular weights), but also disclose Helicobacter pylori proteins with relative molecular weights that read on the claimed proteins in light of the fact that SDS-PAGE gel electrophoresis establishes a relative, approximate, apparent molecular weight for the protein. Evidence for this art recognized understanding is provided by the following patents:

Berget et al (US Pat. 4,957,739, issued Sep. 18, 1990) teaches "Molecular weight assignments are approximate by correlating the SDS gel migration of antigens to the migration of proteins of known molecular weights. Thus, differences in techniques for measuring migration distances will result in differences in apparent molecular weights. These differences are naturally accentuated by the fact that SDS polyacrylamide gel electrophoresis is an inherently less accurate means of determining the molecular weight of larger proteins (see col. 5, lines 36-44).";

Keith et al (US Pat. 4,883,761, issued Nov. 28, 1989) teaches "[T]he comparison of the molecular weights also shows good correspondence to the experimentally-determined values, with slight differences for the S1 (less than 10%) and the S5 (about 15%) subunits. These small differences are within acceptable limits for protein molecular weights determined by SDS-PAGE (see col. 16, lines 7-13)".

Simcox et al (US Pat. 6,054,307) provides evidence that different methods of determining apparent relative molecular weight for the same protein results in different approximate molecular weights: "[T]hus, the approximate molecular weight of FPLC purified SrfI restriction endonuclease was determined to be 55 kd based on Superose 12 column gel filtration and 64 kd based on SDS-Page (see col. 9, lines 63-67 and col. 10, lines 1-22, especially lines 19-22)" .

All of the applied prior art references disclose protein antigens with the recited relative molecular weights or are within the acceptable range of variance for an apparently molecular weight determined by SDS-PAGE gel electrophoresis. The applied references isolated and

purified Helicobacter pylori proteins from whole cell lysate compositions; additional isolation and/purification steps were used to determine the proteins produced by Helicobacter pylori, specifically the proteins apparent relative molecular weight in kilodaltons (kDa). The claimed proteins have not been distinguished from the proteins of the prior art applied against the claims. The rejections made of record are maintained.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
April 17, 2003

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